

A Discussion With
Dr. Norman Radtke
March 5 - 18, 2001
Topic: Retinal Transplantation

Dr. Norman D. Radtke, M.D., F.A.C.S., is a Clinical Professor in the Department of Ophthalmology and Adjunct Associate Research Scientist in the Center for Applied Microcirculatory Research at the University of Louisville in Louisville, Kentucky. He received his B.S. degree from the U.S. Naval Academy in 1964 and his M.D. degree from the University of Michigan Medical School in 1974, and his office is located at the Retina Vitreous Resource Center in Louisville.

Dr. Radtke holds memberships in 19 scientific societies, including the American Medical Association, the Retina Society, the Vitreous Society, and the American Academy of Ophthalmology. Since 1974, he has published a total of 40 articles in every major ophthalmological journal, he has been awarded 16 research and grant awards, and he has participated in 10 multicenter clinical studies. In high demand as a speaker, Dr. Radtke has presented more than 80 lectures throughout the United States and abroad, most recently on the subject of retinal transplantation. In April of this year, he will make a presentation on that subject at the annual convention of the Association for Research in Vision and Ophthalmology (ARVO) in Fort Lauderdale, Florida.

Dr. Radtke has received numerous recognitions for his research and civic activities, but he has still found time to be a dedicated husband of 29 years to Chris, and a father to their two children, Erika and Tyson.

(Edited for length and clarity)

DAN: Dr. Radtke, welcome to our Internet MD Community. We greatly appreciate your offer to spend the next two weeks with us. There are hundreds of people here from not only MDList, but from RPList and MDForum, as well, and we look forward to hearing the latest about the research being done in the area of macular transplantation.

The most recent information we have is an article which I wrote for our library in October of 1999, in which I mentioned the Institute of Ophthalmology's experiments with transplanting cells from the legs of rats into their own retinas (directed by Professor Ray Lund). I also wrote that immunosuppressive drugs had been successful in blocking transplant rejection (in studies being done in St. Louis and Chicago), but that there had not been significant improvement in any are of the human subjects' vision, specifically visual field, dark adaptation threshold, contrast sensitivity, reading speed, maculoscope ERG, and acuity on the Snellen chart. Please bring us up to date on this information.

And, for the benefit of those who may not have been following the research, it would be helpful to first have a description of the purpose and procedure of retinal cell transplantation. You may find it useful to refer to the diagrams on our Eye Anatomy page at <http://www.mdsupport.org/anatomy.html>.

Cell transplantation holds some exciting promise for people with retinal disease, and I hope you will have some good news to bring us. We also welcome any responses you might have to questions about related subjects, since we know that your expertise covers a wide spectrum.

The floor is yours, Dr. Radtke, and thank you for joining us.

DR. RADTKE: Thank you for allowing us to participate in your website. The purpose of retinal cell transplantation is that in diseases such as retinitis pigmentosa and dry macular degeneration, retinal pigment epithelium and the photoreceptors (rods and cones) degenerate. Our intent is to replace them with new cells that integrate with the functional part of the recipient retina that is still working which are the ganglion cells. Hopefully, this will restore vision to those people who have this area missing in their retina. Our procedure is to transplant sheets of fetal retinal pigment epithelium and neural retina in the space where these normally grow and are now nonfunctioning. The hope is that they will grow into a normal adult tissue and hook up with the ganglion cells to restore function.

In our article in the American Journal of Ophthalmology (September 1999, Pages 384-397), we have shown that there was an indication of objective improvement on the multifocal ERG test of the single layer of tissue implanted which was neural retina in one patient at four months. This electrical test did not persist on subsequent months.

Our new efforts have been to transplant two layers of intact sheets of fetal retina with retinal pigment epithelium, and at ARVO 2000 (abstract #528), we have shown that synapses occur between the transplant and the host retina. This study provided anatomical evidence that the sheets of fetal retina and retinal pigment epithelial transplants form synaptic connections with degenerated host retinas. A second publication at ARVO 2000 (abstract #4542), we indicated that the intact fetal sheets of transplanted retinal pigment epithelium and neural retina in a degenerated retina mediated visual evoked responses in the superior colliculus and suggests that the transplants form connections with the host retinas. We stimulated with light a blind rat's eye with a transplant and were able to record an electrical response in the brain in the appropriate quadrant which correlated with the quadrant of the eye in which the transplant was located. The other quadrants where there was no transplant did not show any electrical response in the brain.

We are now placing fetal sheets of retinal pigment epithelium and neural retina in humans with retinitis pigmentosa and have five patients at this time with two patients now at six months out and neither have shown rejection. At this time, the multifocal ERG function is being tested.

Because safety has been shown, the FDA has given us permission to now do transplants in patients who have retinitis pigmentosa and dry macular degeneration who have visual acuity of 20/800 in one eye, where previously we were doing it in patients who had light perception or no light perception in both eyes.

We feel that our technique has significant advantages over preceding efforts. The fetal tissue seems to be tolerated immunologically as they lack antigenic sites. They have a high capacity to proliferate and sprout processes, and they produce trophic substances. We also have a very short time from harvest of the tissue to transplantation which is now four to five hours. Our method of placement, we feel, is less traumatic to the tissue than previous techniques used. We are able to use a specially-designed instrument that allows the surgeon to "draw" the fetal tissue into sleeve-supported mandrel for placement into the host retina. The surgeon is able to position the instrument under the retina, and by releasing a toggle lock, the sleeve is retracted, leaving the fetal tissue under the retina in the desired location. This new technique will allow less damage to occur to the cells prior to placement, as we do not roll the retinal pigment epithelial cells or push them out of the instrument. It is also our feeling that the fetal tissue has a greater ability to overcome the trauma of transplantation than an adult or cultured cells.

At this time, we are recruiting patients for further transplantation and the results of our work to date will be presented at ARVO 2001 (abstract #4994) on May 4, 2001.

DAN: Thank you for that excellent update on your research. I'm glad to hear that rejection of the transplanted tissue seems to no longer be problematic, and that there is now evidence of improvement in visual response. This is good news for people with RP and dry MD, who have not previously had a viable treatment.

Since retinal transplantation uses retinal pigment epithelium from a healthy host with a different set of DNA, am I correct in assuming that the disease will not eventually overtake the new tissue?

If this is true, then retinal transplantation could be the next best thing to DNA replacement for halting cell degeneration, with the added benefit of actually restoring sight.

I saw a video (produced at Washington University in St. Louis) of the surgical procedure using the new technology which you described, and it is indeed impressive. There seems to be some excellent progress in this field, and I hope you get a good response to your patient recruitment for further study.

DR. RADTKE: That is a very good question about what will happen to the disease process if these new transplanted fetal cells are present. It may be that with a different set of DNA, the disease would not eventually overtake the new tissue. At this time, we really do not know. It is one of the things that we will be evaluating. The video that you saw at Washington University in St. Louis is of an instrument that is different than the one we are using. That one has a tube and pushes the cells out. That causes damage to the cells because they are folded, as well as trauma to

the cells when they are pushed out. Our particular instrument has a flat silicone sleeve over a mandrel and allows placement of the tissue as we withdraw the sleeve, rather than pushing the tissue out of the sleeve with the mandrel.

There is a lot going on in this field, and we hope that we can continue to make advances so patients with retinitis pigmentosa and dry macular degeneration do have a future return of their vision. At this time, however, there are still a lot of obstacles to overcome before that is a reality.

JUDY: I assume you are referring to human fetal tissue cells? Are these sheets of fetal retinal pigment epithelium taken from an aborted fetus, or a fetus of a miscarriage?

A miscarriage usually happens in the first trimester of a woman's pregnancy. Would these fetal cells be developed or mature enough to be transplanted? Or are these fetal cells taken with an amniocentesis during a normal pregnancy?

DR. RADTKE: I was referring to human fetal tissue cells that were implanted into the humans. These are sheets of fetal retinal neural tissue and retinal pigment epithelium that are taken from an aborted fetus. We do not take these from fetuses of miscarriages, because miscarriages usually have a reason for a miscarriage, and sometimes those are genetic defects. Fetal cells from the donors that we get are usually between the 10 to 12 week gestation period. No fetal cells are taken from amniocentesis during a normal pregnancy.

JUDY: What are your guidelines for the testing of the woman's donor's blood prior to abortion?

DR. RADTKE: The guidelines for testing of the woman's donor blood prior to the abortion is that we do HIV, hepatitis A, B, and C, syphilis tests, and whether donor is Rh positive or negative. These tests are all gotten back to us prior to our using the tissue for the research in patient implantation.

JUDY: Do you look for the possibility of the donor having a type of transmissible or communicable disease such as HIV, hepatitis B, tuberculosis etc.?

DR. RADTKE: You have accurately assessed the risk for communicable and transmittable diseases. We do test the donor's blood as mentioned above. Additionally, the fluid surrounding the implanted tissue is tested for sterility and endotoxin levels.

JUDY: Do you test for the possibility of an addiction to legal or illegal substances?

DR. RADTKE: We do evaluate for the possibility of addiction to legal or illegal substances. We do this in the social history. The patient is screened, and if there is any evidence of this kind of behavior, obviously we do not use the tissue.

JUDY: Is there a cut off point for the age of the doner? Would a younger woman be preferable, say under the age of 35?

DR. RADTKE: At this time, we have not used an age cutoff for the donor. The woman, certainly, must be 21 or older to be a donor, and we have not addressed the issue about the maximum age and are only concerned about the gestational age of the fetus. The donor is not compensated in any way and her anonymity is protected.

JUDY: Finally, who oversees the obvious moral, ethical considerations for this type of research? I realize there is a fine line to walk, but we need all the help we can get though your laborious work.

DR. RADTKE: The FDA oversees the use of fetal tissue for research, and we must follow strict guidelines, as well as the federal, state, and local laws regarding this. We also undergo close scrutiny by the University of Louisville Human Studies Committee and the IRB Committees at Norton Audubon Hospital and Jewish Hospital to ensure that the moral ethical considerations for this type of research are adhered to. We have received negative press on our efforts by the Right to Life people, but our answer to critics in this regard is that this tissue would otherwise be discarded, and we hope that, in the future, if this shows to be promising, that substitute tissue for this fetal tissue can be developed.

ERV: I am an AMD patient with a dry and a wet eye. There was a conversion to wet one year ago after thermal laser treatment as a CAPT participant. Since then, the eye has stablized, most of the blood has cleared away, and my retinal doctor describes the scar tissue as a blister. I am 20/200 in the damaged eye. Optic nerves are healthy in both eyes, and I am performing normal visual funtions, because the dry eye is relatively healthy. I have glaucoma in both eyes. Would you comment on my condition, and can a blister be treated? I will be 77 next month.

DR. RADTKE: There is nothing else, I think, that can be done in your right eye at this time, and a blister cannot be treated. The fact that you have glaucoma but have healthy optic nerves would be your primary concern, and at this time, I would not recommend any therapy in either eye, other than maintaining your glaucoma medications and following with your doctor for your glaucoma problem.

DR. JEN: Erv, Dr. Radtke used an interesting phrase with you, that "nothing more can be done." I am glad that he chose to word his post this way, as it is something that retina specialists, glaucoma specialists, and even general optometrists and ophthalmologists tell their patients every day, though this is only half true. No medical or surgical treatment can bring back the vision that was lost at this moment in time, however much CAN be done. Low vision rehab is that avenue, and by exploring your options through visiting your local low vision doctor or contacting your state blindness association, you can learn how to use the vision that you do have more efficiently, learn to cope with the psychological aspects of vision loss, meet others with similar vision situations, and above all, learn new ways to do the tasks that enable you to preserve your independence.

It is unfortunate that most doctors just end their statements with "nothing more can be done" instead of telling the whole story of "nothing more can be medically done, but there is so much more out there to help you, here is the card of a low vision specialist who I know will work hard to meet your visual needs, our staff will call his/her office and schedule an appointment for you." The fact that no one ever mentioned low vision rehab to my patients until they stumbled upon it on their own is a point of great frustration with them.

DR. RADTKE: I agree with you 100% that physicians should say "nothing more can be done medically but there is a lot that can be done with low vision aids". We refer all of our patients who have poor vision for low vision aid assistance, and many of them have had excellent results with people who are doing this type of work.

I applaud your efforts in this regard and in no way want to convey an idea that we are not aware of this or ignore its importance to our patients with poor vision from any cause. The contribution that you are making to patients who have age-related macular degeneration is tremendous, vital and deserves special recognition. It is good that you have brought this to my attention, and I will make sure that I am one doctor who never ends a statement by saying "nothing more can be done." I have always tried to do this with our patients and in no way want to take away what can be done by low vision rehabilitation. Contacting the state blindness associations also has been wonderful for our patients, and they have gone to patients' homes and have shown them how to live in their own environment with the vision that they have and to cope with this problem so that they can remain independent of family and friends. Coping with the psychological effects of vision loss with support groups to encourage others who are dealing with the same problem, or even a worse problem, and to learn new ways to preserve their independence are all extremely vital and important. Again, I cannot applaud you enough for your efforts on this behalf.

You can be assured that our patients do not have to stumble upon it on their own, and this is one point of frustration that we will remove from their life.

DR. JEN: It is refreshing to hear you say these things on the list! I just wonder what more I can do with the local ODs and OMDs in the area to convince them of the same. A few have done much better since I have a couple very vocal patients that were blunt in asking why they were not referred for low vision services, but the majority have not come around yet. Do you have any suggestions?

I also agree about state blind associations. In my mind, it is not important where a person goes to get the services, as long as their needs are met. In fact, I will not see any patient who is a veteran...I send them straight to the local VA Blind Center. Why should they pay me, when they can get the same services at no charge? We are blessed, in this part of PA, with wonderful blind associations and a good state system.

MAGGIE: I was originally diagnosed with dry MD by an ophthalmologist. Recently, a retinologist told me I have angioid streaks (idiopathic). He said I did not have "garden variety" MD. Are angioid streaks an elite form of MD? My doctor said it was better to have these streaks than to have MD but from what I have read, I fail to see how. I have no drusen and there has been no bleeding in my eyes. I have had no change in my vision, during the past two years. My acuity remains at 20/25.

DR. RADTKE: Angioid streaks are the retinal manifestation of a systemic problem with collagen and the term is called pseudoxanthoma elasticum. The problem with the collagen is that it occurs in other parts of the body and has a varying degree of symptoms. Age-related macular degeneration and angioid streaks often have subretinal neovascular membranes, although the subretinal neovascular membranes from angioid streaks do not inevitably fall into the macular area and cause decreased vision, as is the case in most situations with age-related macular degeneration. If the bleeding occurs in the center of your vision with angioid streaks, obviously it is as bad as having macular degeneration, but the odds of it occurring there are not as great with angioid streaks. So, the reasoning for the comment by your eye doctor that it is better to have angioid streaks than age-related macular degeneration is probably accurate.

Angioid streaks can progress, however, and should be followed. There are ways of treating angioid streaks that develop bleeding sites which your ophthalmologist can describe to you if he feels you would be a candidate for treatment.

FRANCES: Is there any hope of removing the blind spot from hot laser? My former ophthalmologist said, when I had successful PDT, "Isn't it too bad they did not have this when your other eye went wet"?

DR. RADTKE: There is no medical hope of removing the blind spot from a hot laser, but there may be a form of low vision aid that can help maximize the potential for vision in this eye. Retinal transplantation is a hope for the future, but at this point, it is still experimental. I would agree that photodynamic therapy would have helped a lot of patients had we had it before April 12, 2000.

ERV: With a wet eye at 20/500, and a blister on the retina, it is not clear to me whether the thermal laser, which probably precipitated my conversion from dry as a CAPT participant, burned the retina. I realize you couldn't know for sure, but is it likely? And, if the callendula I am using orally and externally, at my homeopath's recommendation, were successful in dissolving the blister and whether vision is retrievable. I will ask my retina doctor when I see him, but I would like your perspective.

DR. RADTKE: It is hard to tell whether or not the thermal laser can work for you, and as you indicated, I do feel that you ought to ask your retinal doctor about that. I do not know anything about callendula, and therefore, I have no comment with regard to whether or not this could resolve the blister and whether or not vision would be retrievable after its use. Again, I think I would refer this to your retinal

doctor to get his expert opinion, because he has your best interests at heart, as well as your medical history and clinical exam.

ERV: My question was not clear. Thermal laser was used on one of my "dry" eyes which converted to wet about six months after the laser treatment. I was/am a participant in the National Eye Institute's CAPT (Complications of Age-related macular degeneration Prevention Trial) study and now am 20/500 in the damaged eye. Is it likely that I have a permanently blind spot as a result of the laser, and is it possible that the blister is obstructing retrievable vision? The CAPT trial removes drusen from dry to learn if the laser treatment decreases the risk of vision loss from AMD.

DR. RADTKE: I am glad you cleared up my misconception about your question, and I hope that this will provide you with some additional information. The fact that you are participating in a National Eye Institute CAPT is a real credit to you and an indication of how unselfish you are to help those who are coming behind you. I am sorry that you ended up with 20/500 vision in that eye, and it is likely that your blind spot will be permanent. A special type of treatment for drusen is under study, and we know that it removes drusen, but we do not know whether or not removing the drusen will prevent subretinal neovascular membranes from growing in the future. There are different levels of intensity of laser in this trial, and I am sure that your protocol and that your treating physician covered these thoroughly and I will not go into the details.

The risks involved in these studies certainly are unavoidable. There is a great deal to be learned, both from what works and what does not work, and we certainly owe you a debt of gratitude for your participation in this. The question is, "how can we help correct this?" Whether or not your blister is obstructing retrievable vision requires your retinal doctor to tell you after an examination. Although I cannot tell from the term "blister" whether or not this is residual serous fluid with a pigment epithelial detachment or just serous fluid present which may resolve. These are things for your retinal doctor to answer for you.

The fact that your dry eye converted to wet six months after laser treatment should be evaluated by your study doctor as to whether or not this was going to happen in spite of the fact that you had laser. It may not be able to be answered until all the patients have been treated and a statistic for a large number of treated versus untreated patients is available. These questions are very important for us all, and again, I am sorry that you had to be one that has poor central vision, but maybe we can offer you something in the future if retinal transplantation proves to be successful and viable.

PEPUKAYE: Is there any scope for the research you are doing (or any other work you may know of in terms of helping patients with Best's disease?

DR. RADTKE: At the present time, our research is not treating patients with Best's disease, but there may be some future potential for this if we can show that retinal transplantation works in these other conditions. At this point, however, we are not

involved with any protocol, and to the best of my knowledge, there is nothing that I know of being done that is actively recruiting Best's disease for research efforts.

DR. WENDY: Have you had any problems with host or graft rejection?

DR. RADTKE: At this time, we are out six months, and we have not seen any evidence of clinical rejection or fluorescein changes indicating rejection. Of course, we do not have any histology at this point from our patients. We are not placing any of our patients on immunosuppressive therapy.

DR. WENDY: Is there a certain position in the macular area where the transplantations do best, for example, foveal or paramacular?

DR. RADTKE: At the present time, the position that we are trying to put our transplants in is in the foveal and parafoveal area. We do not know if there is a certain position that the transplantation will do best.

DR. WENDY: Is there a chance of macular detachments or holes as a result of transplantation or is there an increased risk for these problems?

DR. RADTKE: There definitely is a chance of macular holes, retinal detachment, loss of the eye from infection, or bleeding. These risks do exist for patients. This is why we initially did the surgery in patients who essentially had little to lose. Patients initially were light perception or no light perception in both eyes. Because of the safety that we have shown to date, the FDA has allowed us to do transplantation on patients with 20/800 vision in the operated eye.

DR. WENDY: In dry macular degeneration patients who receive transplantation, do drusen disappear or do fewer drusen form or do they stay the same?

DR. RADTKE: At this time, we have no information about the effect of drusen on patients who have undergone transplantation. There is no information regarding whether they disappear, whether new drusen form, or whether they stay the same.

DR. WENDY: Do any pigmentary changes, more or less or no change, occur in the transplanted area?

DR. RADTKE: At the present time, we are seeing the transplant increase in size in some patients, and in some patients, the transplant pigment becomes less. Just because the pigment becomes less does not mean that the transplant is dying, it just means that the pigment is not being reproduced in the new cells. We have two or three patients who have shown a marked increase in size of the transplant pigmentation area over a period of three months.

DR. WENDY: Have you used the Scanning Laser Ophthalmoscope (SLO) before and after transplantation to objectively compare the function of the cells of the macula?

DR. RADTKE: We are in the process of using the Scanning Laser Ophthalmoscope in one patient after transplantation, but we do not have that instrument. We are using in its place a multifocal ERG which we have assessed to be more accurate in determining the information that we need regarding the transplant than the Scanning Laser Ophthalmoscope. This information was discussed extensively before we obtained the multifocal ERG. We considered the Scanning Laser Ophthalmoscope, but based upon conversations with people in this field, particularly in Europe where they have had a lot of experience with both of these, we determined that the ERG was better for our purpose at this time.

DR. WENDY: Can fluorescein be used to help map the area of transplantation?

DR. RADTKE: The fluorescein can be used to help us determine whether or not there is any leakage, and it does help us to identify the area of the transplant.

DR. WENDY: For RP, does transplantation of adult photoreceptors work better or worse or the same as fetal retinal cells?

DR. RADTKE: For retinitis pigmentosa, adult photoreceptors do not work as well as fetal retinal cells, and the reason being that the fetal cells are tolerated immunologically as they lack angiogenic sites, they have a high capacity to proliferate and sprout processes, they produce trophic substances, and they have a greater ability to overcome trauma of transplantation than either the adult or cultured cells.

DR. WENDY: How can you test if the transplanted cells communicate and work with the host retinal cells?

DR. RADTKE: We have tested the transplanted cells in animals and shown that they synapse with the ganglion cells and they work with the host retinal cells in animals. At the present time, in humans, we cannot see whether or not they communicate because we cannot do histology, but our multifocal ERG testing is one way that we try to determine if the cells communicate and work with the host retinal cells. In animals, we have shown that by injecting the superior colliculus with a virus, it migrates down the neural pathways to the transplanted area, and we have seen this staining of this pathway on rats. We have also done electrical stimulation of a blind rat transplanted with neural retina and retinal pigment epithelial cells, and we have demonstrated that the intact fetal retinal sheets transplanted in a degenerated retina mediate a visual evoked response in the superior colliculus. When the light stimulated the area of the transplant in the blind rat, there was an electrical response in the appropriate corresponding area of the superior colliculus in the brain of the rat.

DR. WENDY: Do you know the cellular process in which the immature rods and cones develop and survive?

DR. RADTKE: It is the interaction between the rods and cones and retinal pigment epithelium. The rods and cones develop and survive with their interaction with the

retinal pigment epithelium, choriocapillaris, and the other retinal cells, such as amacrine bipolar horizontal Mueller and ganglion cells. The exact cellular process of how they each interact is not completely known.

DAN: In a discussion a while back with Dr. Peter Gouras (Columbia University), I asked, "What can you tell us about the success rate of submacular surgery? Would you recommend this treatment?"

He replied: "... Unless we tie it in with transplantation in the future, I cannot see it going very far...Submacular surgery has not been that useful in older people with MD."

Several of our subscribers have had success with this procedure, and others are considering it. Please comment on Dr. Gouras' response, especially in regards to tying it in with macular transplantation.

DR. RADTKE: I quite agree that the majority of patients do not benefit from this procedure. However, I have had some patients who have benefited from it, and his comment, "unless we tie it in with transplantation in the future, I cannot see it going very far", probably has some truth to it.

At the present time, we are experimentally transplanting patients who have had submacular surgery in the past and have had subsequent loss of the retinal pigment epithelium. These patients are part of our study group and we will have more information on that at a later time.

The people who are considering submacular surgery should talk with the surgeon who is doing the procedure and discuss the issues specifically that they have with that individual. It is difficult to make a broad generalization, and there is a submacular surgery trial going on nationally to assess this.

MAGGIE: I recently had a biopsy for pseudoxanthoma elasticum, and my dermatologist said the results were negative. Does this mean that I probably still have a systemic problem with collagen that is manifesting itself through my retinal streaks? I do not have sickle cell or thalassemia, two other conditions that I understand often accompany streaks.

DR. RADTKE: Angioid streaks, as you know, are breaks in Bruch's membranes caused by various conditions. The elastic lamina that occupies the middle segment of Bruch's membrane is primarily the effect resulting in disintegrating and fraying of the elastic fibers. All cases of angioid streaks that have been studied histopathologically have shown identical changes despite different underlying systemic diseases. The initiating stimulation for the calcification and degeneration of Bruch's membrane in patients with angioid streaks is not yet known. The most common systemic disease associated with angioid streaks is pseudoxanthoma elasticum, and the fact that you have had a negative biopsy for this rules out the most common cause. Between 8% and 15% of patients with Paget's disease of the bone (osteitis deformans) will have angioid streaks as well.

You have ruled out sickle cell or thalassemia, and that is, as you mentioned, two other conditions that can accompany streaks. Other conditions that your medical doctor may want to evaluate and are systemic conditions that are associated with angioid streaks include abetalipoproteinemia, acromegaly, Ehlers-Danlos syndrome, diabetes, facial angiomas, hemochromatosis, hemolytic anemia acquired, hereditary spherocytosis, hypercalcaemia, hyperphosphatemia, lead poisoning, myopia, neurofibromatosis, Paget's disease of the bone, pseudoxanthoma elasticum, senile elastosis, sickle cell disease, Sturge-Weber syndrome, and tuberous sclerosis. Some of these associations may represent coincidental occurrences.

The workup for systemic disease in patients with angioid streaks such as yourself should include the skin biopsy (which you have already had), a serum alkaline phosphatase, calcium and phosphate studies, and a hemoglobin electrophoresis. This is probably more than you wanted to know, and there may be some things that I have missed, but this should pretty much cover all the common causes.

DR. COLE: I've enjoyed your interaction over the last few days. Actually, there's a lot going on right now to address the issue of referrals, i.e. trying to make certain that patients with the need for Vision Rehabilitation Services are in fact referred for these services. I don't want to go on a long dissertation now . . . but I would like to mention a few things:

The Josephine L. Taylor Leadership Institute will be meeting this Friday, Saturday, and Sunday. . . The topics will have a lot to do with the issue of getting services to the patient and getting the patient to the services. I will be participating in a panel this Friday, following Dr. Kupfer's talk, and both will be webcast (and I believe archived on AFB's website for future listening/viewing).

Another major program to address the issue is being run by the National Eye Institute. The NEHEP (National Eye Health Education Program) is targeting low vision as one of its three major areas (diabetes and glaucoma being the other two). It already has a program geared to the patient. Another part of this program will be geared toward healthcare providers. Among other things, there will be an information packet sent to all optometrists and ophthalmologists (about 50,000) stressing the need for referral. Included will be a poster that can be hung in the office reminding them of the importance of referral for low vision services. This is still being developed, but you should be hearing more about it in the near future. And that's only two. Both the American Optometric Association and the American Academy of Ophthalmology are working on this problem. In fact, there was a summit at the American Academy of Ophthalmology's annual meeting that addressed this issue for about 2.5 hours. Representatives of optometry, ophthalmology, AFB, AER, and other organizations were there. This ties in with NEI's program, also.

At the local level, it's really important that you keep getting the message out, both to patients ("consumers") and to the eye/health care professionals ("providers"). And, of course, I really believe that the Internet and sites like MDSupport.org will play a bigger and more important role in dealing with this issue. There will

always be people who are just developing the condition who need help, guidance, and support. Think about how much we know about conditions that we don't have and that haven't affected someone close to us. We would go through some of the same things that people with new ARMD are going through. It will never be perfect, but we can make it a lot better. We just have to keep plugging away at it. Well, I've rattled on long enough...and I'm sure there's more that I could say. But I hope this at least starts in addressing the concerns that you so rightly stated.

SHARON: Your research and implications for those with MD is most exciting. I read today via Medscape that there is a class action suit trying to stop the use of fetal stem cell research. Does this impact on your study, now or in the future? Are you concerned that a new administration in your country could change the laws with reference to use of fetal tissue?

DR. RADTKE: I was not aware of the class action suit trying to stop the use of fetal stem cell research. At the present time, we do not have government funds to support this research, so we are not impacted on the fact that NIH will not support it at this time. What this class action suit means for private funding I do not know. At the present time, we do hope that the new administration does not change the laws with reference to fetal tissue use, but as I mentioned, we are now funded with private funds, and though this would impact us in getting any NIH funds, it would not impact us with our present funding source.

SHARON: Do you have any experience with research on idiopathic polypoidal choroidal vasculopathy? It is my understanding that more and more this is being accepted as a variant of MD. I note that your research is for those with Dry MD. This implies to me that those with wet MD need to accept that little is presently being offered now, or in the future, other than laser and TTT. Is this correct.

DR. RADTKE: I do not have any experience with the research on idiopathic polypoidal choroidal vasculopathy, other than I have two patients with this disease. Whether or not it is a variant of macular degeneration or a separate entity certainly is a question that people are trying to address at this time. At the present time, our research does affect macular degeneration patients in that, when we take out the net surgically, we are often left with absence of retinal pigment epithelium. We are testing patients who have met the visual acuity criteria of 20/800 and have had the nets removed and will be experimenting by replacing the retinal pigment epithelium and neural retina in these patients. We can update you as our results become available.

DR. WENDY: Does the length of time since having been diagnosed with Macular Degeneration decrease the effectiveness of the transplantation? At the present time, we do not have an answer to whether or not the length of time after having been diagnosed with macular degeneration would impact on the effectiveness of transplantation. This, obviously, would be a very important question, and at this time, we are not at a point to answer it.

DR. WENDY: If time is a key factor, what is the optimum time to do the transplantation? If we can show rescue of the ganglion cells in patients whose photoreceptors and pigment epithelium are degenerating, it would be a valuable assessment as to what is the optimum time to do the transplantation. At this point, we do not have that information. We will be working toward answering this question in the future.

DR. WENDY: Does transplanting two layers of intact sheets of fetal retina with RPE cells increase the chances of the RPE cells alligning properly and filling in for missing RPE cells and other tissue?

DR. RADTKE: The transplanting of two layers of intact sheets of fetal retina with RPE cells definitely increases the chance of the RPE cells aligning properly and filling in for missing RPE cells and other tissue. This is a very critical point, and I feel that this is an excellent question. We addressed this in animals seven years ago and felt that without sheets we would get rosette formations if we only injected patches or suspensions or aggregates of RPE cells. You are, in fact, very accurate in assessing that sheets do give increased chances of functioning in retinal transplantation.

DR. WENDY: Do RPE cells that may be damaged when placing the transplant proliferate and cause problems with the transplant or reduce the other cells ability to migrate and replace lost or damaged RPE cells of the host?

DR. RADTKE: At the present time, the damaged RPE cells would probably die and not pose a problem with reducing the other cells' ability to migrate or replace lost or damaged RPE cells of the host. They would, however, if enough were lost, decrease the potential for the growth of the tissue. With our technique, we hope that we minimize damage and also that fetal cells are more apt to be able to withstand the trauma of a transplant, and so the number of RPE cells that survive will probably determine the ability of the transplant to thrive.

DR. WENDY: Do you feel that the degenerated macular cells in Macular Degeneration are dead, toxic, or dormant?

DR. RADTKE: We feel that the degenerated RPE cells and rods and cones of macular degeneration are dead or dying, but that the potential exists for the transplanted fetal RPE and neural cells to hook up with healthier amacrine, bipolar, and ganglion cells.

DR. WENDY: The Foundation Fighting Blindness has called for standardized visual function tests. I agree with this so research results can be compared apples to apples and oranges to oranges. When checking visual acuity, what chart do you use?

DR. RADTKE: When checking visual acuity, we use the Snellen chart, but for our patients, we use multifocal ERG testing. We do not feel that the patients would be able to use the Snellen chart accurately and multifocal ERG will assess the electrical activity in very small areas of the retina and we can compare the area of the

transplanted retina to areas of the surrounding area which are not transplanted and compare the electrical activity. I agree that standardized visual function tests are important so research results can be compared accurately from one kind of study to another.

DR. WENDY: How many lines of visual improvement on the ETDRS chart would you consider to be clinically significant?

DR. RADTKE: At this time, if our patients would see one line of visual improvement on the ETDRS chart we would consider that to be clinically significant.

DR. WENDY: Over the six months of your research, have the transplants remained stable?

DR. RADTKE: The transplants have remained stable in that there has been no rejection, and we have had two transplants increase in size, relative to the amount of pigment that is present, and the other three have shown depigmentation. Depigmentation does not mean that the RPE cells are dying. It means they could be reproducing without pigmentation as is often seen in RPE cultures in the lab.

DR. WENDY: Is a length of time less than six months significant clinically, for example one month, two months?

DR. RADTKE: At the present time, we expect that the maturation of the rods and cones so that they could hook up with the functioning ganglion cells would take approximately four months in humans. It is very important for us to do testing on a month to month basis over the first six months, so that we could see any changes occurring as we do not know for sure that it is going to happen on this time frame. The problem that we have in our present study is that many of the patients live a long distance away, so we feel that our follow-up of one week, six weeks, one month, three months, six months, and one year, we will be able to identify clinically significant times, but this may change as our research progresses.

DR. WENDY: Have the ERG's stayed stable, have they improved, or do the a-wave and b-wave's amplitude and timing, and oscillatory potential amplitudes vary or are they reduced?

DR. RADTKE: At the present time, the multifocal ERG's have remained stable in our present cogafting of the intact sheets of fetal retina and RPE cells in patients with retinitis pigmentosa. We are now moving forward into other stages, such as vision of 20/800 and patients who have central areolar pigment epithelial atrophy and patients who have had wet macular degeneration with removal of the net but with RPE also missing. In all of these patients, we are awaiting what our multifocal ERG's will reveal with regard to all the specifics you just mentioned.

DR. WENDY: Over the course of the study, have you seen a decrease in peripheral neovascularization, if it was present prior to the transplantation?

DR. RADTKE: At the present time, we have not noted any change in the peripheral neovascularization, as in our patients it was not present prior to transplantation.

DR. WENDY: If peripheral retinal neovascularization is present, are all ERG waves reduced in amplitude as they would be without the transplant?

DR. RADTKE: All of the patients that we are seeing at this time do not have any peripheral retinal neovascularization.

DR. WENDY: How long do you feel it will be before you will be treating the average macular degeneration patient?

DR. RADTKE: At the present time, we are taking the first steps in a long climb up a very very high mountain, and there is no way to predict how long it would be before we would be treating the average macular degeneration patient. This will, no doubt, require parallel work in the laboratory and the clinic and would include such things as stem cell and growth factor augmentation of the retinal transplantation. These things are being evaluated in parallel with our clinical studies, and as we get information in the research lab, we will try to be applying this to the clinical setting. This, again, is a long, long journey, and we are just beginning it.